Toward practical application of tumor-immune system analysis (Theory of Biomathematics and Its Applications XI)

AUTHOR(S):

高瀬, 光雄

CITATION:

高瀬, 光雄. Toward practical application of tumor-immune system analysis (Theory of Biomathematics and Its Applications XI). 数理解析研究所講究録 2015, 1937: 171-178: KJ00009782403.

ISSUE DATE:

2015-04

URL:

http://hdl.handle.net/2433/223713

数理解析研究所講究録
第1937巻 2015年 171-178

Toward practical application of tumor-immune system analysis

Mitsuo Takase
LINFOPS Inc.
1-21-1-503 Oukurayama Kouhoku-ku Yokohama 222-0037 Japan
E-mail GZL03154@nifty.com

Abstract. The tumor-immune system interaction seems to be able to be expressed mechanically, mathematically. to a large extent. One of main aims here is to express the state of tumor-immune system mechanically, analytically and quantitatively, and another is to make strategies to cure by making the practical numerical model and its software. Analytical methods and its software which gives us concrete numbers to be able to be applied to treatments in the tumor-immune system have a possibility to give information which can not be obtained without them. This analysis is eigenvalue analysis, and the local ignition at eigenvalue $\lambda = 1$ has a special meaning for the cure. The distance to the local ignition is also important where treatments to make the distance smaller or zero should be made. Here, the behaviors under the sub-ignition state to cure and the movement mechanism from the sub-ignition to the local ignition with the control mechanism of the immune system are shown. The effect of the tendency for tumor cells to tend to become less differentiated and more independent is inspected.

1. Introduction

As tumor- immune system interaction has the aspects of information processing and dymamic system. One of the aims here is to express the interaction mechanically, mathematically, analytically and quantitatively. One of main aims here is to express the state of tumor-immune system in such a way, and another is to make strategies to cure by making the practical numerical model and its software.

An analytical method and its software which gives us concrete numbers to be applied to treatments have a possibility to give information which can not be obtained without them.

Moreover, its discrete numerical analysis with the numerical model and the use of Monte Carlo simulation are considered, and its computer software is being developed for the calculation of the model. This situation leads to the numerical realization of the phenomena and gives us the quantitative analysis by a discrete numerical simulation even if there are not enough mathematical equations.

Here, one of main aims is a practical application which means the realization of the numerical total model and its concrete numerical useful results.

This modeling and their simulations are widely conducted in the areas like power plants.

The numerical simulation can be realized by limiting the simulation area like Extended field model shown in section 2 in the solid tumor although the route to lymph nodes and from them is taken into account. These analytical conditions give us the eigenvalue problem situation and characteristics like eigenvalues greater than 1 or not and quantitative values like to the distance to eigenvalue $\lambda = 1$ although the eigenvalue problem situation varies. Here the state $\lambda = 1$ is named local ignition where the immune system is activated abruptly and locally. So we can inspect various conditions to reach the local ignition to cure. One of characteristics of this analysis is that contact probability between a tumor peptide and T cell receptor is considered to have an equal effect with affinity between a tumor peptide and T cell receptor and killing probability. They give the same effect to achieve the local ignition.
Here, The effect of T cells are mainly considered, this is due to the largeness of the T cell effect to tumor (ref. 2).

Many of these contents are already expressed in ref. 1, 5 and 6. Here, they are arranged and shown

with additional explanation to aim for practical application and the production of the computer software. The practical application is a key aim here.

Moreover, the following two themes are inspected. (1) and (2) are shown in section 3 and 4 respectively.

(1) The behavior and the effects of the immune system to attack a solid tumor in the state of sub-ignition, which means here the state where the local ignition is not yet achieved $\lambda < 1$, is shown. The behaviors under the sub-ignition state to cure and the movement mechanism from the sub-ignition to the local ignition with the control mechanism of the immune system are also shown.

(2) Tumor cells tend to not only evolve to overcome and survive the state of bad conditional environments around them where there are less oxygen, less nutrition and much waste but also become the state less and less differentiated gradually.

The less differentiated and more independent tumor cells are inspected. In the beginning of the tumor, the state of tumor cells can be thought to be differentiated like the healthy cells, then the behavior of T cells in the immune system appears to be clear, but in the state less differentiated and more independent, the behavior and the analysis seem to become much more complicated.

2. The basic model to realize aims

2.1 Explanation of the model

The basic model to realize these aims is shown in Fig. 1 .

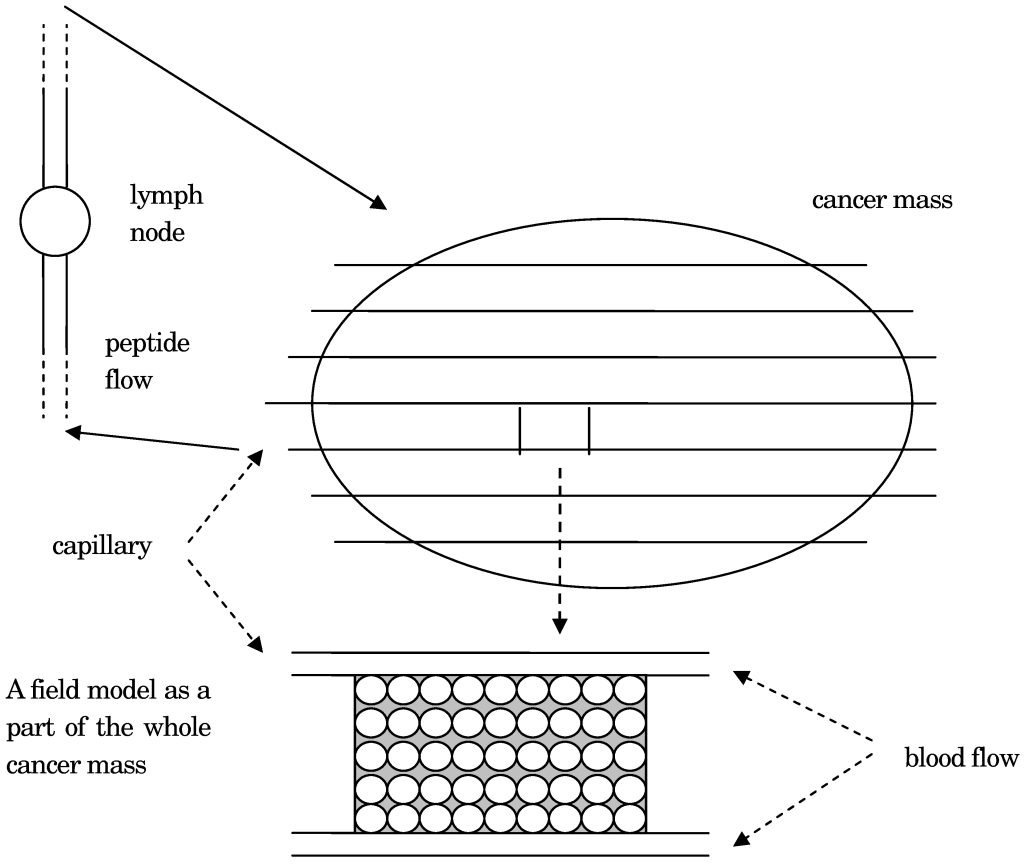

Fig. 1 A field model and its relationship with the whole cancer mass and a lymph node

The area where the analysis should be conducted is shown in the following as Extended field model.

Extended field model ・・・an area where adjacent field models are included and T cells concentration, etc. are statistically much less variable with nearly zero fluctuation by input and output T cells

Field model ・・・an area with the common environment useful for an efficient calculation as shown in Fig. 1.

「Input data」

- Mean free path of T cell
- Averaged frequency of T cell movement
- The concentration of T cells which have higher affinities to the tumor peptide around the solid tumor ・・・[T]
- Initial distribution of tumor cells etc.

「Output data」

- Maximum eigenvalue ・・・This means Tact cell (activated T cell) proliferation rate, etc.
- Eigenvector ・・・proliferation speed spatial distribution of Tact cell concentration [Tact], etc.. The distribution shape and scale gradually change.

The basic model is a comparably small area which determines the environment and the eigenvalue problem from it where we can get characteristically and quantitatively important data not to be obtained without the model.

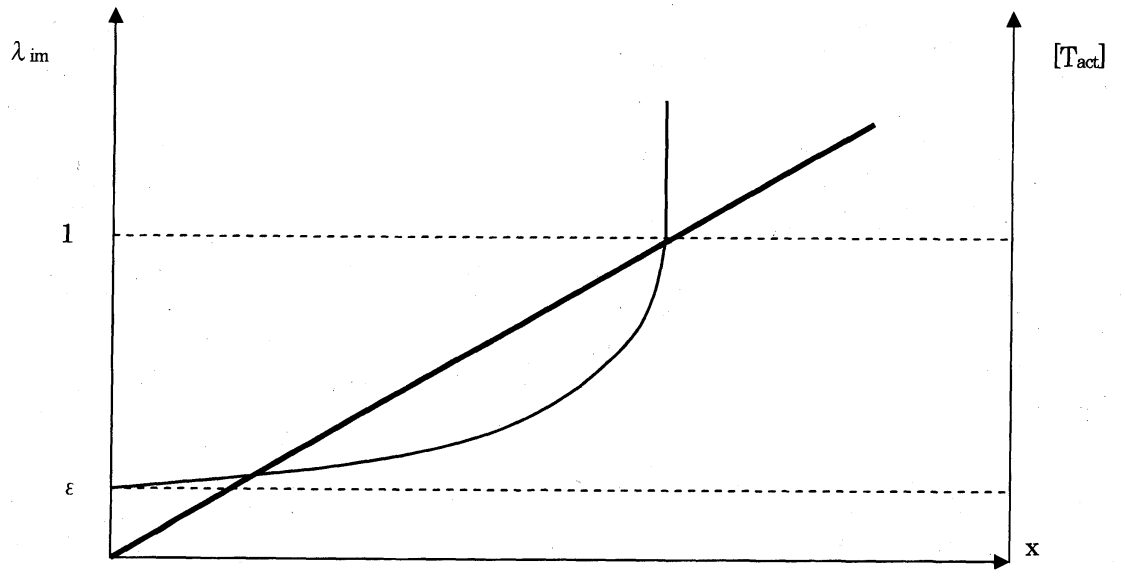

Fig. 2 λ_{im} v.s. x and T_{act} v.s. x graphs. Here x is total effect to increase λ_{im} like [IL2]

——— ・・・ λ_{im}

——— ・・・ [T_{act}]

x ・・・ Total effect to increase λ_{im} like [IL2]

ε ・・・ Entering Th cells and Tc cells with a high affinity into the field model constantly to a cancer peptide

λ_{im} ・・・The T cells proliferation rate which is the eigenvalue of the eigenvalue problem shown in equation (1) in section 2.1.

[Tact] ・・・The concentration of activated T cells which is, for example, the number of T cells per unit volume

[IL2] ・・・The concentration of interleukin 2

[Characteristics of the model]

（1）Availability of input data

The input data should be known by inspection like blood inspection for the practical application

At least the input data of the model are contained in blood.

（2）T cell activation and its works as effector T cells are caused through the multiplication of α、β and γ

$\alpha \times \beta \times \gamma$

α ・・・・・contact probability between T cell and an antigen (tumor peptide)

β ・・・・・affinity of T cell receptors to the tumor peptide

γ ・・・・・probability to kill tumor cell after the contact and the affinity are achieved

From this mechanism T cell movements and the environment where T cells move easily have almost the same effect with the affinity, T cell concentration, etc. to increase the effect of T cells which are increased by vaccine therapy and to achieve the local ignition.

（3）Eigenvalue calculation・・・As the eigenvector changes gradually, the equation of the eigenvalue problem gradually changes.

・Characteristic meaning

・The achievement of eigenvalue $\lambda = 1$ (Fig. 2) is named local ignition here.

・Quantitative meaning

・The distance to $\lambda = 1$ to cause the local ignition has an important value to cure (Fig. 2)..

・Movement of eigenvector

It is thought that these are due to mainly IL2 which is a common element to proliferate T cells like in Fig. 3 and secreted commonly by Tact (activated T cells) cells.

「Additional explanation of the local ignition」

（1）The logical connection has positive feedback loops.

（2）Abrupt proliferation of Tact cells is caused by the achievement of λ=1.

（3）The local ignition has a similarity with association in the brain

（4）There seem often positive feedbacks in immune cells which cause the local ignition like T cells with IL2 like in Fig. 3.

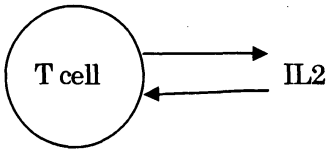

Fig. 3 Positive feedback relationship

2.2 An example of expected control mechanism

An example of expected control mechanism is shown in Fig. 4.

「The effects of the model and the analysis」

(1) T cell movement (mean free path and movement frequency) affects the contact probability between tumor cell peptides and T cell receptors, and the contact probability is considered to have an equal effect with affinity between a tumor peptide and T cell receptor. They give the same effect to achieve the local ignition like shown in section 2.1.

(2) On the other hand, a therapy like vaccine therapy (ref. 3) is thought to increase the affinity and T cell concentration [T]. IL2 therapy (ref. 4) increases the concentration [IL2] and enhance the proliferation rate of T cells as shown in Fig. 3. If some therapies which affect the T cell movements and heighten them, they contribute to heighten T cell activity and to achieve the local ignition.

If some set of multiple therapies lead to the increase of eigenvalue and to the state of the local

ignition, it can have a big meaning for the cure. The multiple therapies can be any therapies including alternative therapies if they have the effects.

(3) By knowing the distance to the local ignition, a concrete aim with a quantitative number can be made, and strategies to approach the local ignition can be planned. If so, this may lead to psychologically better effect.

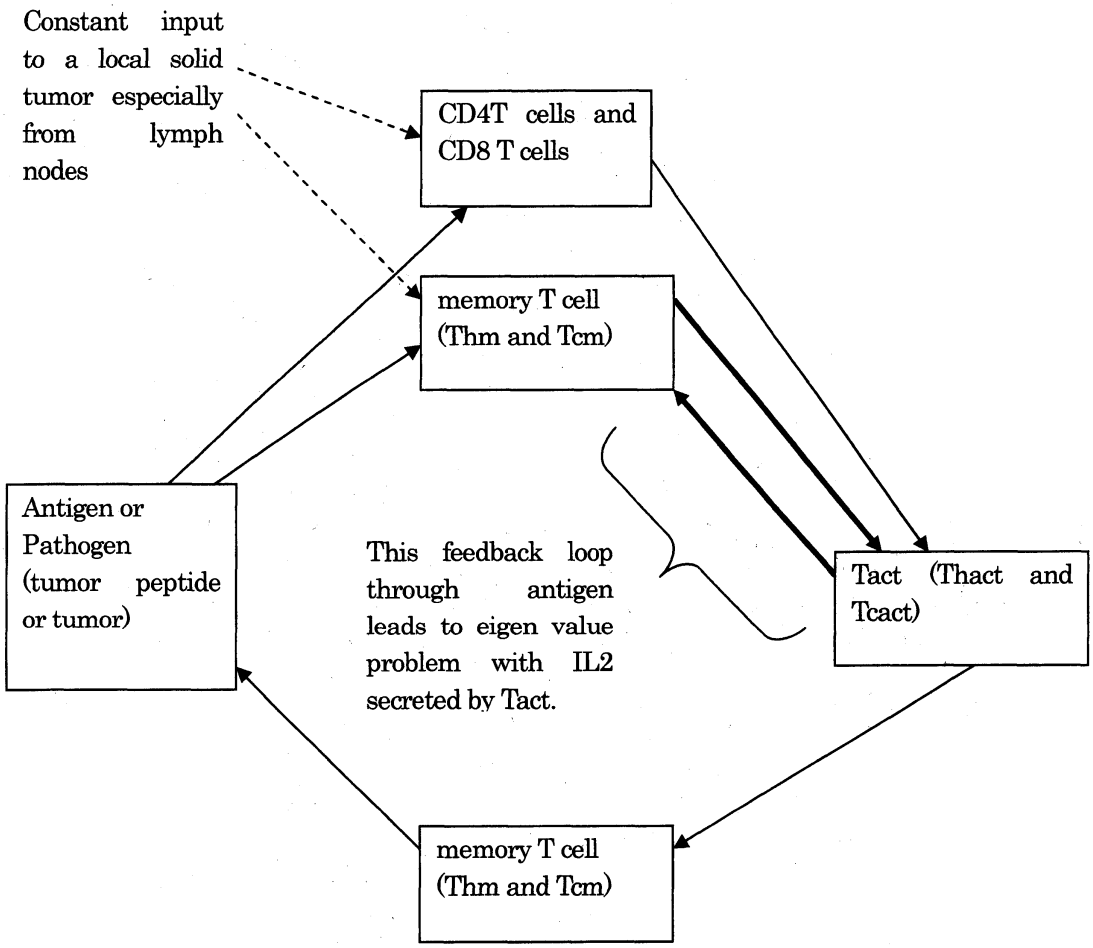

Fig. 4 An example of mechanism to cause the local ignition

Thact・・・activated CD4 T cell

Tcact・・・activated CD8 T cell

Thm ・・・memory CD4 T cell

Tcm ・・・memory CD8 T cell

3. Behavior in the state of sub-ignition, and move to the state of the local ignition and its automatic control

3.1 Behavior in the state of sub-ignition

the behavior and the effects of the immune system to attack the solid tumor in the state of sub-ignition, which means here the state where the local ignition is not yet achieved $\lambda < 1$, is

discussed. If the proliferation rate of tumor cells is enough low, the state of the sub-ignition may have an enough ability to eliminate the solid tumor. This state can be expressed by the following equations. The behaviors can be inferred from the equation to a certain extent.

Equation (1) is expressed by eigenvalue problem expression.

λ_{im} means eigenvalue which is the growth of eigenvector.

$$\lambda_{im}\begin{Bmatrix}\{Tact\}\\ \{T\}\\ \{Tm\}\end{Bmatrix} = \begin{bmatrix} A1 & B1 & Bm1\\ B2 & A2 & [0]\\ Bm2 & [0] & A3\end{bmatrix}\begin{Bmatrix}\{Tact\}\\ \{T\}\\ \{Tm\}\end{Bmatrix} \quad \cdots (1)$$

Equation (2) is expressed by recurrent form meaning the same phenomena of equation (1)

{T}, {Tact} and {Tm} in equation (1) and {Teffe} in equation (2) can include both cases of CD4T and CD8T. Here the expressions are simplified in equation (1) and (2).

T ・・・T cell

Tact ・・・activated T cell

Tm ・・・memory T cell

Teffe ・・・effector T cell

Each element Ti of {T} means the concentration of T cells at position i which means the number of T cells in a unit volume at position i.

Here for example B1 submatrix depends on tumor cells and can be expressed by like

$B1 = b_1 \cdot E \cdot \{C\}$ where b1 is constant and depends on the T cell movement and the affinity between T cell receptor and tumor cell peptides

{C} ・・・tumor cells concentration distribution like (T)

E ・・・unit matrix

$$\begin{Bmatrix}\{Tact\}\\ \{T\}\\ \{Tm\}\end{Bmatrix}_{i+1} = \begin{bmatrix} A1 & B1 & Bm1\\ B2 & A2 & [0]\\ Bm2 & [0] & A3\end{bmatrix}\begin{Bmatrix}\{Tact\}\\ \{T\}\\ \{Tm\}\end{Bmatrix}_{i} \quad \cdots (2)$$

$$\begin{Bmatrix}\{Tact\}\\ \{T\}\\ \{Tm\}\\ \{Teffe\}\end{Bmatrix}_{i+1} = \begin{bmatrix} A1 & B1 & Bm1 & [0]\\ B2 & A2 & [0] & [0]\\ Bm2 & [0] & A3 & [0]\\ B3 & [0] & [0] & A4\end{bmatrix}\begin{Bmatrix}\{Tact\}\\ \{T\}\\ \{Tm\}\\ \{Teffe\}\end{Bmatrix}_{i} \quad \cdots (3)$$

$$\{C\}_{i+1} = \lambda c \cdot E \cdot \{C\}_i - \alpha \cdot (E \cdot \{Tceffe\}) \cdot \{C\}_i$$

$$= (\lambda c \cdot E - \alpha \cdot (E \cdot \{Tceffe\})) \cdot \{C\}_i \quad \cdots (4)$$

Tceffe ・・・effector T cell of CD8T cell which means cytotoxic T cell often expressed by CTL. This means Teffe in equation (3).

λc ・・・The proliferation rate of tumor cells without any suppression by the immune system.

Equation (4) shows the dynamic behavior with the suppression by T cells, and for λc to be enough small in comparison with $\| \{Tceffe\} \|$ can cause the deletion of tumor cells by T cells under the sub-ignition.

$$\lambda_{c2}\{C\} = (\lambda c \cdot E - \alpha \cdot (E \cdot \{Tceffe\})) \cdot \{C\} \quad \cdots (5)$$

λ_{c2} ・・・ the proliferation rate of tumor cells with the suppression by Tceffe cells.

Equation (5) means eigenvalue problem expression of equation (4). $\lambda_{c2} < 1$ which means the decrease of the tumor cells can be achieved.

3.2 Move to the state of the local ignition and its automatic control

If the proliferation rate of tumor cells is enough low for T cells to delete the tumor cells completely under the sub-ignition, the tumor cells disappear and the disease will be completely cured.

When the tumor cells proliferate more and more although T cells attack the tumor cells under the sub-ignition even if λ_{im} becomes bigger and bigger under the sub-ignition, it is necessary for λ_{im} to achieve the local ignition.

When the local ignition is achieved, the concentration of the activated T cells [T_{act}] becomes larger and larger without limit theoretically beyond the point where the proliferation rate λ_{c2} of tumor cells become less than 1 for the tumor to become smaller until the tumor cells are completely deleted or nearly completely deleted theoretically..

At that time, as shown in Fig.4, when there is no tumor cell for the positive feedback to be maintained, and the positive feedback disappears.

Here, these show the example of the automatic control mechanism of the immune system by T cells according to the existence of tumor cells..

At the process from the sub-ignition to the local ignition, the clear recognition of the existence of tumor cells by T cells is necessary. The clear recognition may not be easy. The some mechanism from reliability about this is shown in ref. 6.

4. A study for why tumors are not easily cured without the achievement of the state of the local ignition by thinking mechanically

Here, we think about one of the reasons why in many cases of solid tumors they can not be cured easily.

(1) Tumor cells tend to become the state less and less differentiated and more independent gradually.

(2) Tumor cells evolve gradually to get abilities like angiogenesis and metastasis surviving the state of bad conditions where there can be less oxygen, less nutrition and much waste materials.

In the case (1), the analysis and the model seem to become complicated abruptly not to catch the dynamic behavior easily and clearly in comparison with the state of differentiated tumor cells which means a comparably early state of tumor as shown in the followings.

「An example」 There is a case where tumor cells tend to present less MHC I and MHC II gradually (ref. 2). Then T cells with α/β receptor can not recognize easily even if they have contact with the tumor cell.

This situation is similar to a lower state of T cell concentration [T] with high affinities.

・NK cells begin to work to kill the tumor cells instead of CTL which is a Teffe cell of a CD8 T cell (ref. 2). NK cells not only work to kill the tumor cells without MHC I , but also effectively kill them by the support of antibodies which are produced by B cells. The situation is named ADCC.

Here the existence of the local ignition is important to cause a strong response of the immune system, but both NK cells and B cells do not seem to have so strong positive feedback as T cells, and IL2 causes the proliferation of both NK cells and B cells, but the local ignition by the set of T cells and IL2 will not be made easily from less MHC I and less MHC II although there are T cells with γ/δ receptor which recognize directly antigen without MHC I and MHC II (ref. 2). These situations are shown in Fig. 5.

If we think about only this situation in Fig. 5 mechanically, the local ignition by T cells and IL2 will become more and more difficult to be achieved, because the positive feedback caused by T cells and IL2 becomes weaker and weaker according to less MHC I and less MHC II (ref. 6).

This situation may mean an actual hurdle to cure even if there is a loop like
NK cell → IFN-γ → Th_1 (type 1 helper T cell) → Tact → IL2 → NK cell proliferation.

So from these mechanical discussions, various methods should be considered enough to heighten the activity..

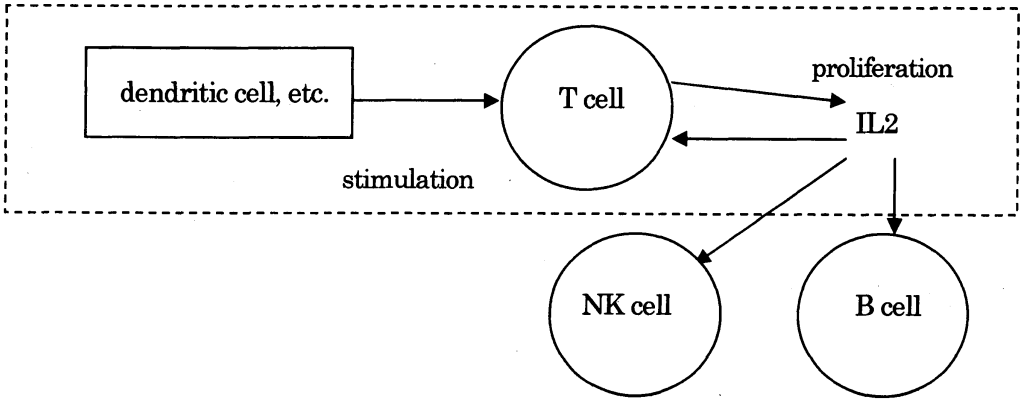

Fig. 5 A simple proliferation and stimulation relationship

5. Discussion

The model is a frame model which will be added more detailed expressions according to necessity although the present model will cover an effective and wide behaviors in the tumor-immune interaction. Moreover, when the detailed expressions will be added, the model is expected to present results nearer to the actual results.

The matrix expression is mainly used here. The expression can have more direct relationship with Monte Carlo simulation method and making the software, moreover it seems to have the ability to express the tumor- immune interaction situation and behavior freely.

In ref. 7, 4 conditions to keep the parts of the body normal are proposed. These seem to be necessary to avoid tumor.

References

1. Takase, M. (2010) Induction and application of an equation to analyze a local ignitionof the immune system for a complete deletion of a cancer mass Theory of Biomathematics and its applications VI. RISM 1704, 53-60 Kyoto University.

2. Charles A. Janeway Jr.et. al., Immuno biology the immune system in health and disease, Garland.

3. Yue Zhang, Y. et al. (2006) Th1 cell adjuvant therapy combined with tumor vaccination. International Immunology 19, 151-161

4. Ewend, M. G. et al. (2000) Intracranial paracrine interleukin 2 therapy stimulates prolonged antitumor immunity that extends outside the central nervous system. Journal of immunology

5. Takase, M. (2009) Cancer and immune system interaction model like a neural network model, analysis of cancer mass effect and meaning of vaccine Theory of Biomathematics and its applications V. RISM 1663, 35-40 Kyoto University.

6. Takase, M. (2013) A automatic control mechanism to ignite the immune system locally against a small cancer mass considering reliability.Theory of Biomathematics and its applications IX. RISM 1853, 185-193 Kyoto University.

7. Takase, M. (2012) Definition of tumor by the loss of stability and functional analytic approach with scale changes for tumor behaviors based on genes.Theory of Biomathematics and its applications VIII.RISM 1796, 158-166 Kyoto University.